Baptist Health

New Frontiers in Breast Oncology

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Objectives

Discuss Pivotal Clinical Trials that lead to approval of oral agents for Breast Cancer in 2023-2024:

Early Breast Cancer

1. Ribociclib for HR +/HER-2 negative

Advanced/Metastatic Breast Cancer

2. Capivasertib for HR +/HER-2 negative,PIK3CA, AKT1, and/or PTEN mutation
3. Inavolisib for HR+/HER-2 negative, PIK3CA mutation
4. Elacestrant for ER+/HER-2 Negative, ESR1 mutation

Clinical Pearls to keep in mind when monitoring patients on these agents

Abbreviations

HR – Hormone Receptor
PR – Progesterone Receptor
ER – Estrogen Receptor
HER-2 – Human Epidermal Growth Factor Receptor 2
NCCN – National Comprehensive Cancer Network
OS – Overall Survival
IDFS – Invasive Disease-free Survival
HR – Hazard Ratio
CI – Confidence Interval
Aromatase Inhibitor (AI)
SERM – Selective Estrogen Receptor Modulator
ADE – Adverse Drug Event
CI – Contraindication
BBW – Black Box Warning
LH – Luteinizing Hormone
LFT – Liver Function Tests
BMS – Bone Marrow Suppression
HS – Hypersensitivity
EP – Emetic Potential
EFS – Event-Free Survival
Ca – Calcium
Mag – Magnesium
K – Potassium
Na – Sodium
VTE – Venous Thromboembolism Event
CDK – Cyclin-Dependent Kinase
ECHO – Echocardiogram
MUGA – Multigated Acquisition
LVEF – Left Ventricular Ejection Fracture

Early Breast Cancer

Updates 2023-2024

Ribociclib Data: NATALEE Trial

Methods	• Open-label, Phase III trial • 426 HR +, HER-2 early breast cancer patients with stage II or III disease off)

Results	• Key Points:
	  • The reduced risk of recurrence with HR +, HER-2 negative early breast cancer patients with stage II-III disease
	  • No new ADEs noted for ribociclib during the trial

September 17, 2024, FDA Update:

FDA approves Ribociclib to be given with AI for patients with HR +, HER-2 -, stage II-III early breast cancer patients with high-risk of recurrence

NOTE: This does include LN – breast cancer patients

Salmon D et al. *N Engl J Med*. 2024;390(12):1080-1091;FDA approves ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer. FDA approves ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer. Updated September 17, 2024.

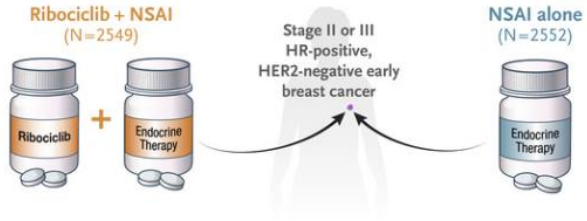
Ribociclib Data: NATALEE Trial

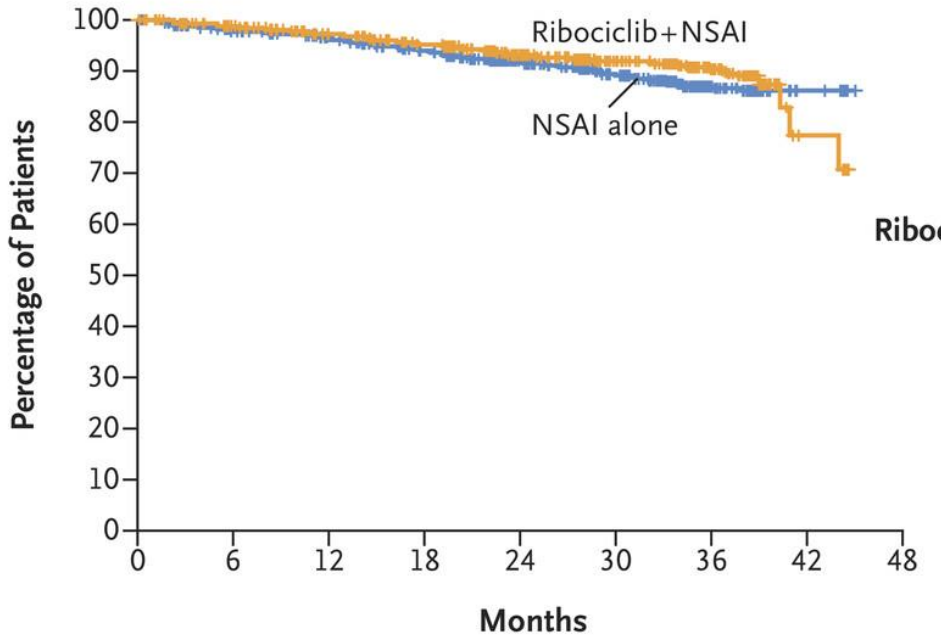
Methods	• Open-label, Phase III trial
	• 426 HR +, HER-2 early breast cancer patients with stage II or III disease
	  • **Patients must have one of the following:**
	  • **Stage IIb-III regardless of LN status**
	  • **Stage IIa + LN positive**
	  • **Stage IIa + Grade 2 tumor + Ki-67 ≥ 20% + LN negative**
	  • **Stage IIa + Grade 3 tumor**
	  • **Stage IIa + Grade 2 tumor + High genomic risk patients (Recurrence score ≥26)**
	• Randomized 1:1 to Nonsteroidal AI + ribociclib 400 mg daily (3 weeks on and 1 week off) for 3 years –OR– Nonsteroidal AI monotherapy

Results	• 3-year IDFS: 90.4% (Combination) vs 87.1% (Nonsteroidal AI monotherapy)
	  • (HR 0.75; 95% CI 0.62-0.91; P=0.003)
	• Key Points:
	  • The reduced risk of recurrence with HR +, HER-2 negative early breast cancer patients with stage II-III disease
	  • No new ADEs noted for ribociclib during the trial

Salmon D et al. *N Engl J Med*. 2024;390(12):1080-1091; FDA approves ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer. FDA approves ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer | Updated September 17, 2024.

Ribociclib Data: NATALEE Trial
Kaplan-Meier Estimates of Invasive Disease-free Survival





	No. of Patients with Event/ Total No. (%)	3-Yr Invasive Disease–free Survival
		percent
Ribociclib+NSAI	189/2549 (7.4)	90.4
NSAI alone	237/2552 (9.3)	87.1

Hazard ratio for invasive disease, recurrence, or death, 0.75 (95% CI, 0.62–0.91)
Two-sided P=0.003

Median follow-up for invasive disease–free survival, 27.7 mo

No. at Risk

Ribociclib+NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

Salmon D et al. *N Engl J Med*. 2024;390(12):1080-1091. FDA approves ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer. FDA approves ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer. Updated September 17, 2024.

Abemaciclib Data: MONARCH-E Trial + Interim Analysis

Methods	• Open-label, Phase III trial
	• 5,637 HR +, HER-2 -, high-risk early breast cancer patients
	  • **Cohort 1 (5,120 patients):**
	  • **≥ 4 positive axillary LN**
	  • **1 to 3 positive axillary LN –AND– Histologic Grade 3**
	  • **1 to 3 positive axillary LN –AND– Tumor ≥ 5 cm**
	  • **Cohort 2 (517 patients):**
	  • **1 to 3 positive axillary LN –AND– Ki-67 ≥ 20%**
	• Randomized 1:1 to endocrine therapy + abemaciclib 150 mg PO twice daily for 2 years –OR– endocrine monotherapy

Results	• 2-year IDFS: 92.2% (Combination) vs 88.7% (Endocrine monotherapy)
	• Interim Analysis at 4 years:
	  • IDFS: 85.8% vs 79.4%
	  • All cause mortality: 5.6% vs 6.1% (HR 0.929; P=0.50)
	  • Common Grade 3/4 ADE: Neutropenia, diarrhea, leukopenia
	• <u>Key Points:</u>
	  • Combination was superior compared to endocrine monotherapy (HR 0.75; 95% CI 0.60-0.93; P=0.01)
	  • The reduced risk of recurrence is sustained after the completion of abemaciclib
	  • No new ADEs noted for abemaciclib during the trial
	  • OS data is immature for cohort 2, and more deaths occurred in combination therapy (4% vs 1.9%)

Johnston SRD et al. *J Clin Oncol*. 2020;38(34):3987-3998. Johnston SRD et al. *Lancet Oncol*. 2023;24(1):77-90.

Cyclin-dependent Kinase (CDK) 4/6 inhibitor

	Ribociclib	Abemaciclib
MOA	• Small molecule CDK inhibitor that targets CDK 4/6 → Prevent the progress of cell cycle in G1 phase by blocking retinoblastoma protein phosphorylation	
Dosing	• 400 mg PO daily (3 weeks on followed by 1 week off) for 3 years • In combination with AI	• 150 mg PO twice daily for 2 years • In combination with endocrine therapy
ADEs	• ≥ 20%: Renal dysfunction, GI upset, headache, increased LFTs, myelosuppression, infection, and fatigue	• ≥ 20%: Renal dysfunction, GI upset, headache, alopecia, myelosuppression, infection, and fatigue
Clinical Pearls	• Dose adjustments needed if eGFR < 30 or Child-Pugh class B or higher • Detailed dose reduction is provided for hepatoxicity during treatment, hematologic toxicities, QTc prolongation, Dermatologic, and pulmonary toxicity • Major CYP3A4 substrate → Avoid strong CYP3A4 inhibitors or inducers	• Dose adjustments needed if > Child-Pugh class C or higher • Detailed dose reduction is provided for VTE events, diarrhea, hematologic toxicities, and pulmonary toxicity • Major CYP3A4 substrate → Avoid strong CYP3A4 inducers and dose reduce for moderate/strong inhibitors

National Comprehensive Cancer Network. Breast Cancer. 2024; ribociclib [package insert]. East Hanover, NJ:Updated September 2024; abemaciclib[package insert]. Indianapolis, IN: Updated January 2024.

Cyclin-dependent Kinase (CDK) 4/6 inhibitor

	Ribociclib	Abemaciclib
MOA	• Small molecule CDK inhibitor that targets CDK 4/6 → Prevent the progress of cell cycle in G1 phase by blocking retinoblastoma protein phosphorylation	
Dosing	• 400 mg PO daily (3 weeks on followed by 1 week off) for 3 years •	• 150 mg PO twice daily for 2 years • In combination with AI
ADEs	•	•
Clinical Pearls	• Dose adjustments needed if eGFR < 30 or Child-Pugh class B or higher • Detailed dose reduction is provided for hepatoxicity during treatment, hematologic toxicities, QTc prolongation, Dermatologic, and pulmonary toxicity • Major CYP3A4 substrate → Avoid strong CYP3A4 inhibitors or inducers	• Detailed dose reduction is provided for VTE events, diarrhea, hematologic toxicities, and pulmonary toxicity • Major CYP3A4 substrate → Avoid strong CYP3A4 inducers and dose reduce for moderate/strong inhibitors

Ribociclib Dose Adjustment Levels	
Target	400 mg PO daily
Level 1	200 mg PO daily
Level 2	Discontinuation

Abemaciclib Dose Adjustment Levels	
Target	150 mg PO twice daily
Level 1	100 mg PO twice daily
Level 2	50 mg PO twice daily
Level 3	Discontinuation

National Comprehensive Cancer Network. Breast Cancer. 2024; ribociclib [package insert]. East Hanover, NJ:Updated September 2024; abemaciclib[package insert]. Indianapolis, IN: Updated January 2024.

Abemaciclib vs. Ribociclib

	Abemaciclib	Ribociclib

Criteria	• HR +, HER-2 -, high-risk early breast cancer patients
	• Patients must have one of the following:
	  • ≥ 4 positive axillary LN
	  • 1 to 3 positive axillary LN –AND– histologic grade 3
	  • 1 to 3 positive axillary LN –AND– tumor ≥ 5 cm
		• HR +, HER-2 early breast cancer patients
		• Patients must have one of the following:
		  • Stage IIb-III regardless of LN status
		  • Stage IIa + LN positive
		  • Stage IIa + Grade 2 tumor + Ki-67 ≥ 20% + LN negative
		  • Stage IIa + Grade 3 tumor
		  • Stage IIa + Grade 2 tumor + High genomic risk patients (Recurrence score ≥26)

Dosing	• 150 mg PO twice daily	• 400 mg PO daily (3 weeks on followed by 1 week off)
Duration	• 2 years	• 3 years
Endocrine Therapy	• AI –OR– tamoxifen +/- ovarian suppression	• AI

Salmon D et al. *N Engl J Med*. 2024;390(12):1080-1091; Johnston SRD et al. *J Clin Oncol*. 2020;38(34):3987-3998.

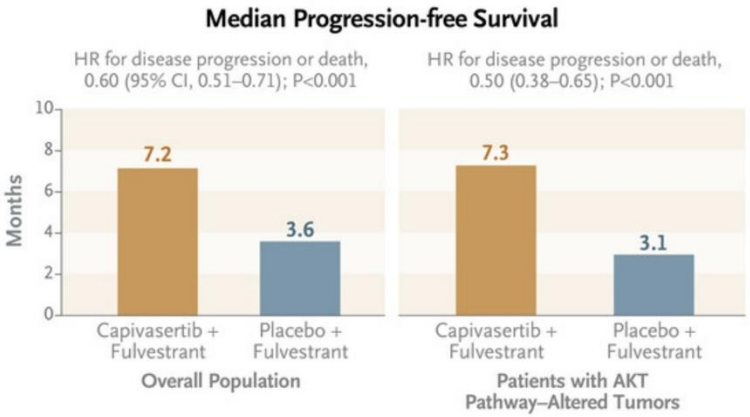
Metastatic Breast Cancer

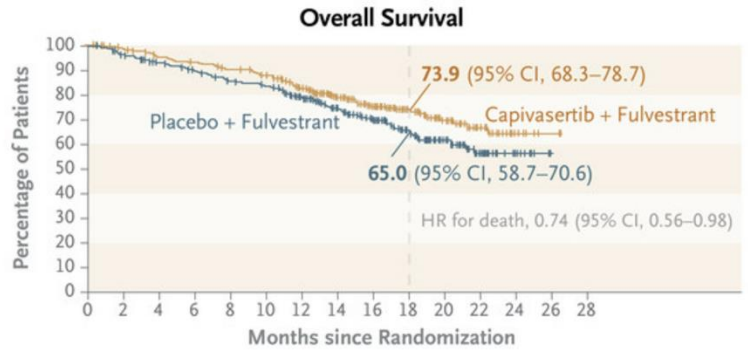
Updates 2023-2024

CAPItello Trial (Capivasertib)

Randomized, double blind, placebo-controlled phase III trial

Participants	Men and postmenopausal women with confirmed HR+/HER2- advanced BC locally advanced or MBC with ≥ 1 PIK3CA/AKT1/PTEN-alterations on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy
Interventions	Capivasertib 400 mg or placebo administered orally twice daily for 4 days, followed by 3 days off treatment each week over a 28-day treatment cycle with + IM Fulvestrant 500 mg intramuscularly on cycle 1 days 1 and 15, and then every 28 days thereafter
Outcomes	Primary: PFS Secondary: OS
Results	PFS was **7.3 months** (95% CI: 5.5, 9.0) in the capivasertib-fulvestrant group and **3.1 months** (95% CI: 2.0, 3.7) in the placebo-fulvestrant group (Hazard Ratio [HR] 0.50 [95% CI: 0.38, 0.65] p-value< 0.0001)

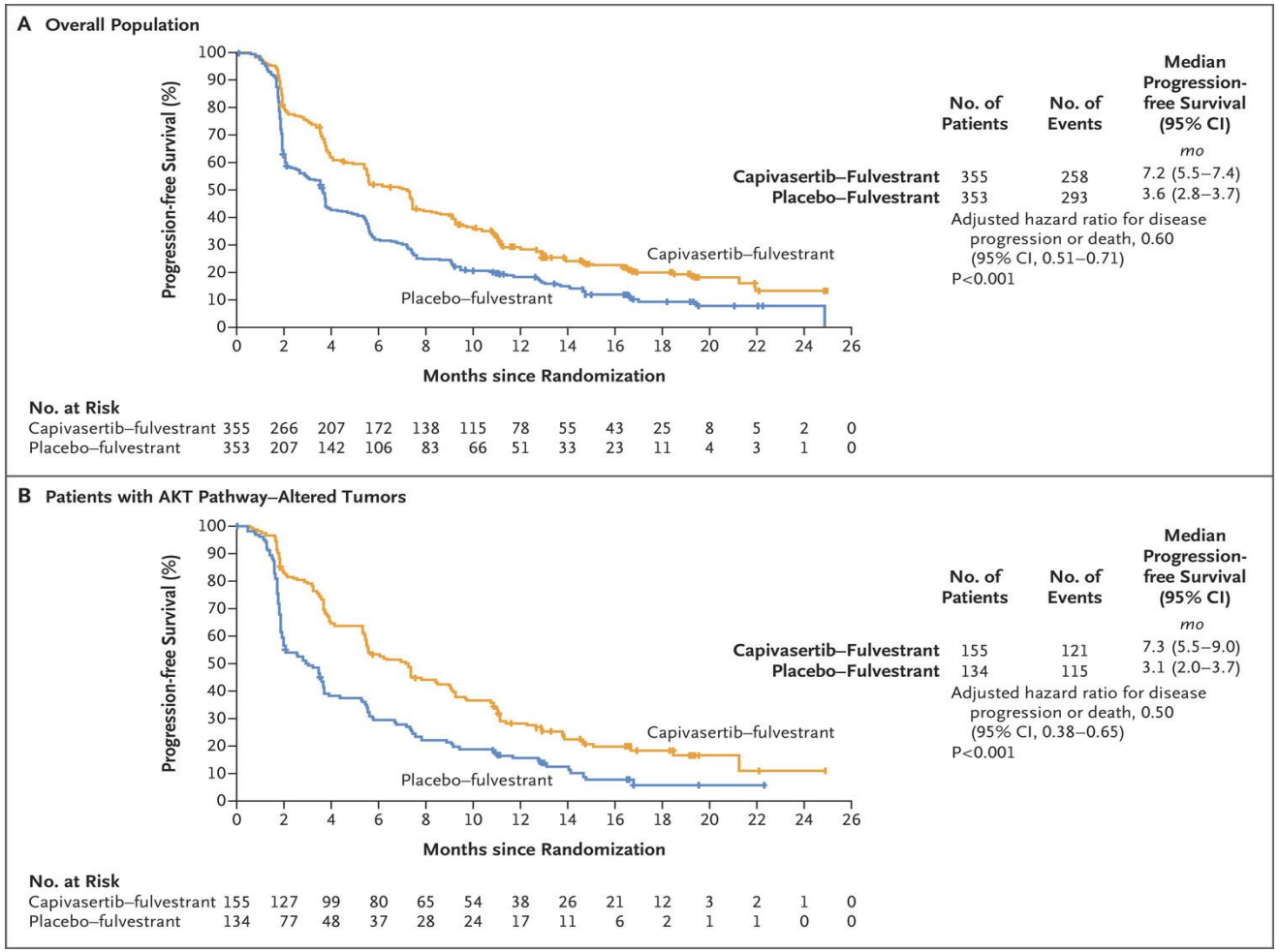




Turner NC, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023.

CAPItello Trial (Capivasertib): Progression-free Survival in Overall population and in Patients with AKT Pathway- Altered Tumors

Randomized, double blind, placebo-controlled phase III trial



Turner NC, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023.

Capivasertib

Dosing (Renal & Hepatic)	Common Adverse Events	Dosing Adjustment for Toxicity	Lab Monitoring & Supportive Care
Locally advanced or metastatic, HR+/HER2-, PIK3CA, AKT1, and/or PTEN altered BC: Oral: 400 mg twice daily (~12 hours apart) for 4 consecutive days, followed by 3 days off (administer on days 1 to 4 of each week); in combination with fulvestrant	• Dermatologic Toxicity (Cutaneous reactions) • GI Toxicity (Diarrhea) • Hyperglycemia • Other Grade 2, 3, or 4 toxicities	**Dose modification levels*:** • 400 mg twice daily (initial) • 320 mg twice daily (1st reduction) • 200 mg twice daily (2nd reduction) ***Discontinue** if unable to tolerate 2nd dose reduction	**Hepatic function** (bilirubin, ALT, AST) prior to treatment **FBG and HbA1c** prior to initiation and periodically during therapy • FBG at least every 2 weeks during the first month and at least once a month starting from the second month, prior to the scheduled dose

capivasertib [prescribing information]. Wilmington, January 2023.

INAVO120 Trial (Inavolisib with Palbociclib and Fulvestrant)

NEWLY APPROVED ON 10/10/24

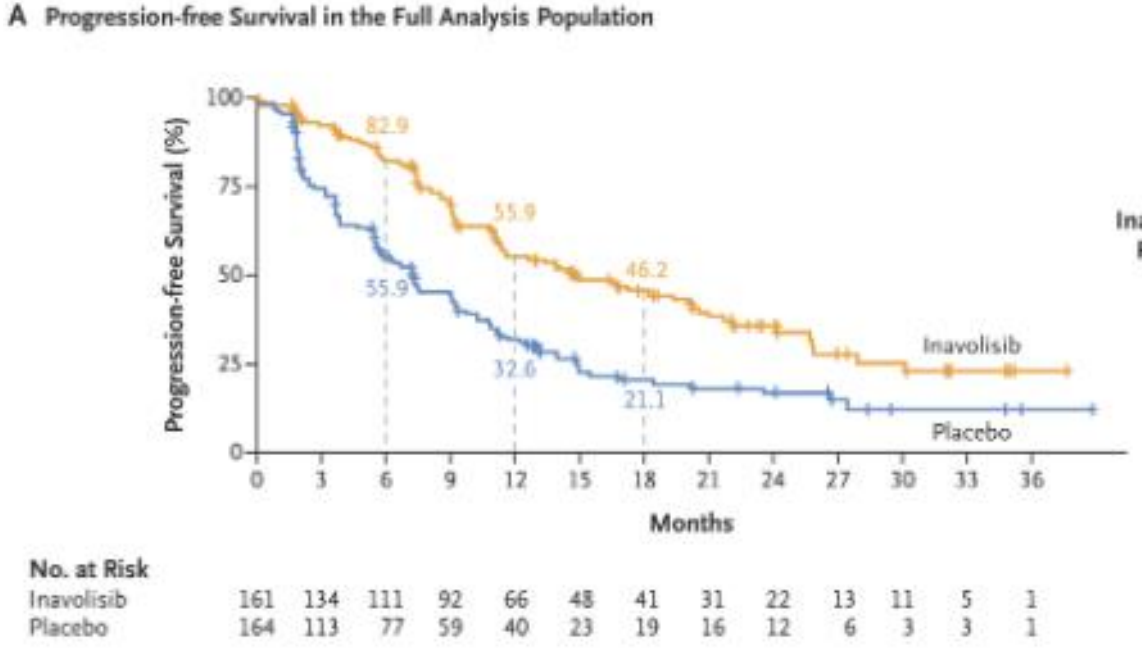
Randomized, double blind, placebo-controlled phase III trial

Participants	Adult patients with endocrine-resistant, PIK3CA-mutated HR+/HER2-negative locally advanced or metastatic BC whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease
Interventions	Inavolisib 9 mg or placebo PO once daily, with palbociclib 125 mg PO once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days, and fulvestrant 500 mg IM Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle
Outcomes	Primary: PFS Secondary: OS, ORR, DOR
Results	Median PFS was **15.0 months** (95% CI: 11.3, 20.5) in the inavolisib + palbociclib + fulvestrant arm and **7.3 months** (95% CI: 5.6, 9.3) in the placebo + palbociclib + fulvestrant arm (Hazard ratio 0.43 [95% CI: 0.32, 0.59] p-value <0.0001)

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer. U.S. Food And Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive. Published October 10, 2024.

INAVO120 Trial: Progression-free Survival

Randomized, double blind, placebo-controlled phase III trial



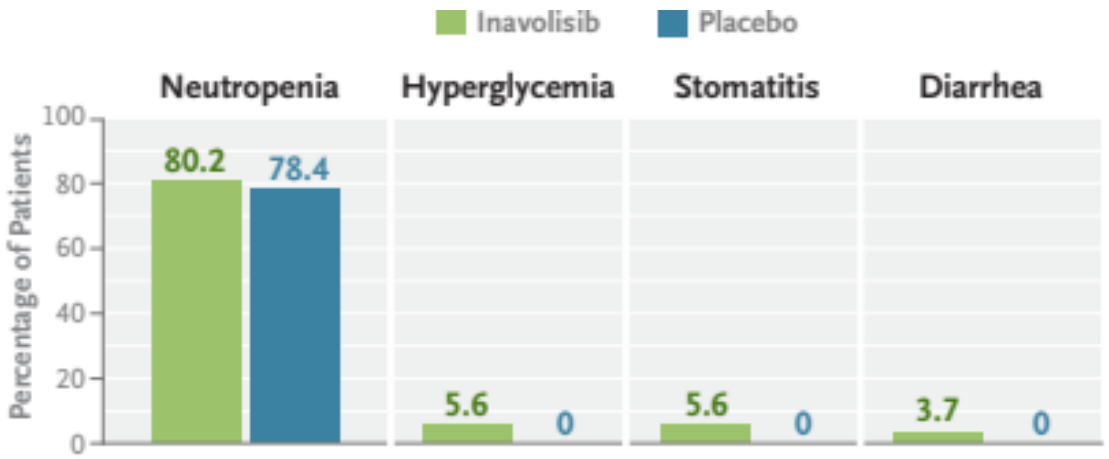
	No. of Events (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	82 (50.9)	15.0 (11.3–20.5)
Placebo (N=164)	113 (68.9)	7.3 (5.6–9.3)

Stratified hazard ratio for disease progression or death, 0.43 (95% CI, 0.32–0.59)
P<0.001

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer. U.S. Food And Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive. Published October 10, 2024.

INAVO120 Trial: Adverse Events

Randomized, double blind, placebo-controlled phase III trial



The incidence of grade 3 or 4 neutropenia was similar in the two groups. Grade 3 or 4 hyperglycemia, stomatitis or mucosal inflammation, and diarrhea occurred in a higher percentage of patients in the inavolisib group than in the placebo group.

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer. U.S. Food And Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive. Published October 10, 2024.

INAVO120 Trial: (Inavolisib with Palbociclib and Fulvestrant)

Randomized, double blind, placebo-controlled phase III trial

Dosing (Renal & Hepatic)	Common Adverse Events	Dosing Adjustment for Toxicity	Lab Monitoring & Supportive Care
Endocrine-resistant, PIK3CA- mutated, HR+/HER2- locally advanced or metastatic BC following recurrence on or after completing adjuvant endocrine therapy Oral: 9 mg once daily in combination with Palbociclib and fulvestrant **Renal Dosing:** eGFR 30-60 mL/min: Reduce dose to 6 mg daily **Anticipated Availability is currently unknown**	• Dermatologic Toxicity (Cutaneous reactions) • GI Toxicity (Diarrhea and Stomatitis) • Hyperglycemia	**Dose modification levels*:** • 9 mg once daily • 6 mg once daily • 3 mg once daily ***Discontinue** if unable to tolerate 2nd dose reduction	**CMP, CBC** **FBG and HbA1c** prior to initiation and periodically during therapy • Monitor FBG levels once every 3 days for the first week then once every week for the next 3 weeks then once every 2 weeks for the next 8 weeks, then once monthly thereafter. Monitor HbA1C every 3 months.

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer. U.S. Food And Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive. Published October 10, 2024.

Emerald Trial (Elacestrant)

Randomized, open-label, phase III trial

Participants	Postmenopausal women with ER+/HER2- advanced BC who: •1-2 lines of endocrine therapy •Pretreatment with a CDK4/6 inhibitor •≤ 1 chemotherapy
Interventions	Randomized 1:1: •Elacestrant 400 mg orally once daily •Standard-of-care (SOC) endocrine monotherapy
Outcomes	Primary: PFS Secondary: OS, ORR, DOR
Results	PFS was prolonged in all patients (HR = 0.70; 95% CI, 0.55 to 0.88; P = .002) and patients with ESR1 mutation (hazard ratio = 0.55; 95% CI, 0.39 to 0.77; P = .0005)

Bidard F, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. Journal of Clinical Oncology. 2022

ESR-1 Mutation: Elacestrant

MOA	• Estrogen receptor antagonist that binds to estrogen receptor-alpha (Erα)
Indication	• Advanced or metastatic, ER+, HER2-, ESR1 mutated (postmenopausal patients or males)
Dose	• 345 mg tablet taken orally, once daily, with food
Adverse Reaction	• Hepatic impairment • Muscle and Joint Pain

Dosing Adjustment for Toxicity	Lab Monitoring & Supportive Care
Dose modification levels*: 345 mg once daily (initial), 258 mg once daily (1st reduction), 172 mg once daily (2nd reduction) ***Discontinue** if unable to tolerate 172 mg once daily	Assess hepatic function; monitor lipid profile **prior to therapy initiation and periodically thereafter**

elacestrant [prescribing information]. New York; January 2023.

References

1. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. doi:10.1200/JCO.20.02514
2. Ribociclib[package insert]. East Hanover, NJ: Updated September 2024.
3. Abemaciclib [package insert]. Indianapolis, IN: Updated January 2024.
4. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90. doi:10.1016/S1470-2045(22)00694-5
5. Slamon D, Lipatov O, Nowecki Z, et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer. *N Engl J Med*. 2024;390(12):1080-1091. doi:10.1056/NEJMoa2305488
6. FDA approves Ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer. FDA approves Ribociclib to reduce risk of recurrence in people with HR+/HER2- early breast cancer | Updated September 17, 2024.
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8. Bidard F, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. Journal of Clinical Oncology. 2022
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10. Inavolisib [package insert]. California: October 2024.
11. Turner NC, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023.
12. Capivasertib [package insert]. Detroit: November 2023.

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